PATENT

P-9565-US

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicants:	SIEGEL, S.J.	Examiner:	FUBARA B.M.
Serial No.:	10/046,504	Group Art Unit:	1618
Filed:	October 19, 2001	Confirmation No.	3358
Title:	POLYMER-BASED SURGICALLY IMPLATABLE HALOPERIDOL DELIVERY SYSTEMS AND METHODS FOR THEIR PRODUCTION AND USE		

DECLARATION UNDER RULE 37 C.F.R. 1.132

Assistant Commissioner for Patents
Washington, DC 20231

I, SIEGEL, Steven, a citizen of United States of America, residing at 86 Highpoint Drive, Berwyn, PA 19312 and a named inventor of the present Application, hereby declare:

1. I am an Associate Professor at the University of Pennsylvania and Director of the Translational Neuroscience Program. I have an M.D. and a Ph.D. in Biomedical Science/Neurobiology from Mount Sinai School of Medicine. My fields of expertise are the Neurobiology and Pharmacology of Schizophrenia, The Clinical management of Psychotic Disorders, Electrophysiology, and Polymer based Drug Delivery. Specifically I have been involved in the study of Clinical studies of the Biological basis of Schizophrenia, Electrophysiological evaluation of candidate genes and neural pathways responsible for the abnormal behaviors and mental processes in schizophrenia,

the acute and lasting consequences of drugs of abuse including ketamine and nicotine, and discovery and development of long term biodegradable polymer drug delivery systems for schizophrenia and other neuropsychiatric disorders.

2. My Curriculum Vitae and list of publications are attached herewith as Appendix 1.

3. I have read the subject Application and have reviewed the patent prosecution history of the subject Application, including all the Office Actions and the references that served as basis for the Examiner's rejection alleging *inter-alia*, that a surgically implantable drug delivery system comprising a biodegradable polymer or copolymer selected from the group consisting of polylactide and lactide-co-glycolide copolymer and 20 to 40% haloperidol is obvious in view of the cited references.

4. Claim 1 of the subject Application recites a surgically implantable drug delivery system, comprising:
   (a) a biodegradable polymer or copolymer, wherein said biodegradable polymer or copolymer consists essentially of polylactide or lactide-co-glycolide copolymer; and
   (b) between about 20 to 40% haloperidol fabricated into an individual, surgically implantable implant via solvent casting and compression molding at a temperature and pressure which allows the haloperidol-polymer material to flow into a mold for the individual, surgically implantable implant which is surgically implanted underneath the skin of a patient, delivers steady state concentrations of haloperidol to the patient for 5 months or more and is removable from the patient in the event the patient exhibits unwanted side effects following implantation

5. Claim 4 of the subject application recites a method of producing an individual, surgically implantable implant which is surgically implanted underneath the skin of a patient for delivery of steady state concentrations of haloperidol to the patient for 5 months or more comprising:

(a) dissolving between about 20% and 40% haloperidol and a biodegradable polymer consisting essentially of polylactide or lactide-co-glycolide copolymer in acetone;

(b) solvent casting the haloperidol and biodegradable polymer solution to produce a completely dry haloperidol-polymer material; and

(c) molding under compression the dry haloperidol-polymer material at a temperature and pressure which allows the haloperidol-polymer material to flow into a mold for the individual, surgically implantable implant which is surgically implanted underneath the skin of a patient, delivers steady state concentrations of haloperidol to the patient for 5 months or more, and is removable following implantation into a patient in the event the patient exhibits unwanted side effects following implantation.

6. The resulting biodegradable implant has a two stage pseudo zero-order release of 20-40% haloperidol into the blood of a patient over a period of about 5 months and is capable of being removed immediately upon the observation and determination of the need to do so due to undesirable side effects.

7. In the Office Action dated January 16, 2008 and the Final Office Action dated September 3, 2008; the Examiner rejected claims 1 and 3 under 35 U.S.C. § 103(a), as being unpatentable over Cheng et al, "A poly(D,L-lactide-co-glycolide) microsphere depot system for delivery of haloperidol," in Journal of Controlled Release 55 (1998) 203-212. The Examiner alleged that Cheng et al., which describes haloperidol-loaded biodegradable poly(D,L-lactide-co-glycolide) (PLG) microsphere (abstract), achieved a 10% haloperidol. Further, the Examiner alleges that the "Surgically implantable drug delivery" is in the preamble and represents the intended use of the delivery system while the body of the claim fully defines the claimed system. The Examiner maintains that Cheng et al., discloses a drug content of from 14.6 to 23.9%, which can allegedly be loaded onto the PLG microspheres and therefore, taking the teaching of Cheng et al., one of ordinary skill in the art at the time the invention was made would have

reasonable expectation of success to formulate haloperidol loaded biodegradable poly(D,L-lactide-co-glycolide) (PLG) microsphere in which the drug load is 10% or from 14.6 to 23.9%.

8. The Examiner is incorrect in her assertions it would not have been obvious for a person skilled in the art to obtain Applicants' claimed invention based on Cheng et al. for the reasons set forth hereinafter.

9. **The Haloperidol/Polymer system disclosed by Cheng et al., cannot achieve the 20-40% Haloperidol concentrations obtained in the implants of the subject application, since the polymer matrix and encapsulated drug form a unique physico-chemical combination with a characteristic release profile.** As shown in Figure 5 of Cheng et al., at higher initial loading of the API, release rate is accelerated, unlike the results described in the present application showing a decrease in release rate with increasing actual initial loading, thereby teaching away from the subject Application. Increased drug flux with increased initial loading is expected (*See* e.g. Menemse GümüsdereliogGlu and Günday Deniz, Journal of Biomaterials Science, Polymer Edition Volume 11, Number 10 / December, 2000, Pages 1039-1050 "Sustained release of mitomycin-C from poly(DL-lactide)/poly(DL-lactide-*co*-glycolide) films" showing that both the rate and the percentage of released MMC increased as the drug load increased from 0.5 to 2 mg MMC per 300 mg of polymer. See also, Sharma, Kuldeepak, 1987 "Mechanisms of Drug Diffusion from Polymeric Devices" Dissertation Abstracts International, Volume: 48-02, Section: B, page: 486, showing that initial drug load, drug loading solvents and the drug polymer interactions affect release of several drugs from devices comprising both hydrophilic and hydrophobic polymers studied showed an increase in release as the initial drug load increased.). In the subject Application, unexpectedly at high Haloperidol concentrations, matrix degradation changes and release rates are affected. As stated in the application on page 3, para. 26, higher Haloperidol loading concentration stabilizes the system, slowing the release rate. This shows in my opinion, that the polymer matrix used by Cheng et al., is substantially different than the polymer matrix used

in the present Application. Likewise any person of ordinary skill in the art, knowing about the effect of the polymer matrix on the encapsulated drug release would not expect the unexpected results in the present Application based on the results disclosed in Cheng et al.

10. **Due to known unique encapsulant/matrix interactions, a person skilled in the art would not draw any conclusions from the encapsulation efficiency of one encapsulant to another in the same polymer matrix.** In my opinion, Cheng et al. does not disclose a surgically implantable drug delivery system comprising a biodegradable polymer or copolymer selected from the group consisting of polylactide and lactide-co-glycolide copolymer and 20 to 40% haloperidol, nor is the disclosure credible considering the unexpected nature of the effects of higher Haloperidol loading on the release rate. Therefore, at the time the invention was made, the results described by Cheng et al. could not have made it obvious for a skilled practitioner that an actual 20-40% loading of Haloperidol in a polylactide or lactide-co-glycolide copolymer, as claimed in the subject Application would give the same or similar loading as 14.6-23.9% of 5-fluorouracyl in a PLG matrix.

The undersigned further declares that all statements made herein of his own knowledge are true, and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made, are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code, and that such willful false statements may jeopardize the validity of the application or any patent issuing thereon.

Date: 2/27/9

Signature

UNIVERSITY OF PENNSYLVANIA - SCHOOL OF MEDICINE
Curriculum Vitae

Updated: July 21, 2008

Steven J. Siegel, M.D., Ph.D.

Office Address: Translational Research Laboratories, Rm. 2223
125 S. 31st Street
Philadelphia PA 19104

Education:

1982-1986	B.A. - Colgate University	Neuroscience
1990 - 1994	Ph.D. - Mount Sinai School of Medicine	Neurobiology
1988 - 1996	M.D. - Medicine Mount Sinai School of Medicine	Medicine

Postgraduate Training and Fellowship Appointments:

1993 John D. & Catherine T. Training Fellowship, Mount Sinai School of Medicine
1994 Charles A. Dana Postdoctoral Fellowship, Mount Sinai School of Medicine
1996-2000 Wistar Scholar and Resident in Psychiatry, University of Pennsylvania
1999-2001 Postdoctoral Fellowship, Neuropsychiatry, Department of Psychiatry, University of Pennsylvania School of Medicine

Military Service:
None

Faculty Appointments:

2001 - 2008 Assistant Professor of Psychiatry, Department of Psychiatry, University of Pennsylvania School of Medicine
2008 - present Associate Professor of Psychiatry with Tenure, Department of Psychiatry, University of Pennsylvania School of Medicine
Director, Clinical Neuroscience Track, School of Medicine
2009 - present Director, Division of Translational Neuroscience

Hospital and Administrative Appointments:

2001 - Present - Attending Physician, Department of Psychiatry, Hospital of the University of Pennsylvania
2001 - Present - Attending Physician, Department of Psychiatry, Presbyterian Medical Center
2007 - Present - Attending Physician, Department of Psychiatry, Pennsylvania Hospital

Other Appointments:

2005 – Present: Member, Institute for Translational Medicine and Therapeutics (ITMAT), University of Pennsylvania School of Medicine
2006 – Present: Member, Abramson Cancer Center

2005 – Present: Faculty member, Neuroscience Graduate Group, University of Pennsylvania – Supervising one Neuroscience Graduate Group PhD rotation student presently. School of Medicine

2005 – Present: Faculty member, Pharmacology Graduate Group, University of Pennsylvania School of Medicine – Supervising one Pharmacology Graduate Group PhD student and one PhD rotation student presently.

2008 – Present: Faculty member, Biomedical Graduate Group, University of Pennsylvania School of Medicine – Supervising one Biomedical Engineering Graduate Group MDPhD student presently.

Specialty Certification: 2001 American Board of Psychiatry
Licensure: Pennsylvania

Awards, Honors and Membership in Honorary Societies:

Edward M. Stimetz Outstanding Freshman Award, Colgate University	1983
Lawrence Organic Chemistry Award, Colgate University	1984
Honors in Neuroscience, Magna Cum Laude, Phi Beta Kappa, Colgate University	1986
NARSAD Young Investigator Award	1998
APA/Organon Excellence in Psychiatry Residency Award	1999
AAP/Bristol-Myers Squibb Fellowship in Academic Psychiatry	2000
APA/Wyeth-Ayerst M.D. Ph.D. Research Fellowship in Psychiatry	2000
ACNP/ Bristol-Myers Squibb Travel Award	2001
APA/Kempf Fund Award	2001
Member, Society for Biological Psychiatry	2002
Member, American College of Neuropsychopharmacology	2004
Exemplary Psychiatrist Award, NAMI	2008

Memberships in Professional & Scientific Societies and Other Professional Activities: (offices held.)

International: None

National:
Society for Neuroscience: 1990 - present
American Psychiatric Association: 1999 - present
National Alliance for the Mentally Ill: 2000 - present
Society for Biological Psychiatry: 2003 – present
American College of Neuropsycopharmacology: 2004 – present
(Program Committee Member: 2008)

Local:
Board of Directors, NAMI PA, Main Line Chapter: 2007 – present

Editorial Positions:
Editorial Board, *Behavioral Neuroscience*

Academic and Institutional Committees:

Experimental Therapeutics Theme Group of SOM Research Coordinating Council, 2003
TRL Animal Users Group Committee

Major Academic and Clinical Teaching Responsibilities:

1. Director, Clinical Neurosciences Track (CNST). Course Director for weekly seminar, summer research and mentoring program for MS 1 – 4 students in CNST, 11/2007 - present
2. Brain and Behavior, MD200B - Psychopharmacology for first year medical students, 2001 - present
3. Antipsychotic pharmacology to PGY 1/2 residents, 2001 - present
4. Antipsychotic pharmacology to PGY 3/4 residents, 2001 - present
5. Schizophrenia lecture in Nursing School: 2001 – 2005
6. Independent Study Faculty Supervisor for 4 undergraduate students in BBB program and 2 students in Engineering as well as one student in Biotechnology Masters Program: 2001 – 2007
7. Senior Design, School of Engineering – Team of three to nine students per year perform design project in my laboratory every year – approximately 1 hr of lecture and 1 hr of supervision per week, 2003 – 2008
8. Animal models – lecture for Pharmacology graduate group, 9/28/06
9. Antipsychotic Medications- lecture for Medical Pharmacology Graduate course PHARMACOLOGY 600: 11/2/06
10. Clinical Supervision for 2 Residents in Psychiatry, 1 each in 2005, 2007 and 2008, 1 hr per week

Lectures by Invitation:

8/6/2003 The use of surgically implantable antipsychotic delivery systems for schizophrenia & Mouse models of schizophrenia using auditory evoked potentials – University of Tasmania, Hobart, Tasmania, Australia,

5/17/2005 Implantable Antipsychotic Medication: The rocky road from necessity to reality, University of Cincinnati, Cincinnati, OH, Grand Rounds

3/16/2006 Nicotine receptor subtype contributions to the beneficial and detrimental effects of nicotine on ERPs, National TTURC grantee conference, Washington, DC

7/19/2006 Animal models of Schizophrenia, University of Tasmania, Hobart, Tasmania Australia

1/9/2007 Nanotechnology and Other Novel Delivery Methods Invited lecture at NIH sponsored conference "Translational Medication Development For Nicotine Dependence Workshop", January 8-10, 2007, Washington, DC

4/13/2007 From Mouse to Man by Way of the Auditory Pathway: The effects of ketamine and nicotine on auditory processing models of schizophrenia, Yale University, New Haven CT

4/23/2007 Event Related brain activity in mice and the alpha 7 nicotine receptor, University of Pittsburgh Medical Center, Pittsburgh, PA

5/16/2007 Using Event Related brain activity in mice to guide medication development: Is there a role for the alpha 7 nicotine receptor?, University of California at San Diego, San Diego, CA

8/28/2007 Electrophysiological Mouse Models of Schizophrenia and Semiannual Antipsychotic Drug Delivery: Balancing Mechanistic Discovery and Real World Action, Aachen, Germany

9/1/2007 PDE inhibitors for treatment of schizophrenia: Invited talk at the European Behavioral Pharmacology Society meeting in Tuebingen, Germany

11/13/2008 – Improving medication adherence in schizophrenia – University of Maryland Medical Center

Organizing Roles in Scientific Meetings:

1. Chair – Symposium "New approaches to improve long-term treatment adherence in Schizophrenia", APA meeting, Chicago, IL, 5/15/2000.
2. Organizer - Symposium on Ethical Issues Regarding Surgically Implantable Medications in Psychiatry, Univ. of Pennsylvania, Philadelphia, Pennsylvania, 12/18/2003
3. INA-WFSBP Congress, Animal models of schizophrenia: A critical assessment of phenotype validation (Session Chair), Athens, Greece – 10/18/2004

Bibliography

Research Publications, peer reviewed (print or other media):

During Graduate Training

1. **Siegel**, S.J., S.D. Ginsberg, P.R. Hof, S.L. Foote, W.G. Young, G.W. Kraemer, W.T. McKinney, and J.H. Morrison, *Effects of social deprivation in prepubescent rhesus monkeys: immunohistochemical analysis of the neurofilament protein triplet in the hippocampal formation.* Brain Res, 1993. **619**(1-2): p. 299-305.
2. **Siegel**, S.J., N. Brose, W.G. Janssen, G.P. Gasic, R. Jahn, S.F. Heinemann, and J.H. Morrison, *Regional, cellular, and ultrastructural distribution of N-methyl-D-aspartate receptor subunit 1 in monkey hippocampus.* Proc Natl Acad Sci U S A, 1994. **91**(2): p. 564-8.
3. **Siegel**, S.J., W.G. Janssen, J.W. Tullai, S.W. Rogers, T. Moran, S.F. Heinemann, and J.H. Morrison, *Distribution of the excitatory amino acid receptor subunits GluR2(4) in monkey hippocampus and colocalization with subunits GluR5-7 and NMDAR1.* J Neurosci, 1995. **15**(4): p. 2707-19.
4. Gazzaley, A.H., S.J. **Siegel**, J.H. Kordower, E.J. Mufson, and J.H. Morrison, *Circuit-specific alterations of N-methyl-D-aspartate receptor subunit 1 in the dentate gyrus of aged monkeys.* Proc Natl Acad Sci U S A, 1996. **93**(7): p. 3121-5.

Fellowship at Penn

5. Gur, R.C., J.D. Ragland, P.J. Moberg, W.B. Bilker, C. Kohler, S.J. **Siegel**, and R.E. Gur, *Computerized neurocognitive scanning: II. The profile of schizophrenia.* Neuropsychopharmacology, 2001. **25**(5): p. 777-88.
6. Gur, R.C., J.D. Ragland, P.J. Moberg, T.H. Turner, W.B. Bilker, C. Kohler, S.J. **Siegel**, and R.E. Gur, *Computerized neurocognitive scanning: I. Methodology and validation in healthy people.* Neuropsychopharmacology, 2001. **25**(5): p. 766-76.

Since joining the faculty as an independent investigator in 2001

7. **Siegel**, S.J., K.I. Winey, R.E. Gur, R.H. Lenox, W.B. Bilker, D. Ikeda, N. Gandhi, and W.X. Zhang, *Surgically implantable long-term antipsychotic delivery systems for the treatment of schizophrenia.* Neuropsychopharmacology, 2002. **26**(6): p. 817-23.
8. Bilker, W.B., C. Brensinger, M.M. Kurtz, C. Kohler, R.C. Gur, S.J. **Siegel**, and R.E. Gur, *Development of an abbreviated schizophrenia quality of life scale using a new method.* Neuropsychopharmacology, 2003. **28**(4): p. 773-7.
9. Connolly, P.M., C.R. Maxwell, S.J. Kanes, T. Abel, Y. Liang, J. Tokarczyk, W.B. Bilker, B.I. Turetsky, R.E. Gur, and S.J. **Siegel**, *Inhibition of auditory evoked potentials and prepulse inhibition of startle in DBA/2J and DBA/2Hsd inbred mouse substrains.* Brain Res, 2003. **992**(1): p. 85-95.
10. Gur, R.E., C. Kohler, J.D. Ragland, S.J. **Siegel**, W.B. Bilker, J. Loughead, N. Phend, and R.C. Gur, *Neurocognitive performance and clinical changes in olanzapine-treated patients with schizophrenia.* Neuropsychopharmacology, 2003. **28**(11): p. 2029-36.
11. Kohler, C.G., T.H. Turner, W.B. Bilker, C.M. Brensinger, S.J. **Siegel**, S.J. Kanes, R.E. Gur, and R.C. Gur, *Facial emotion recognition in schizophrenia: intensity effects and error pattern.* Am J Psychiatry, 2003. **160**(10): p. 1768-74.
12. Moberg, P.J., S.E. Arnold, R.L. Doty, C. Kohler, S. Kanes, S. **Siegel**, R.E. Gur, and B.I. Turetsky, *Impairment of odor hedonics in men with schizophrenia.* Am J Psychiatry, 2003. **160**(10): p. 1784-9.
13. Ragland, J.D., S.T. Moelter, C. McGrath, S.K. Hill, R.E. Gur, W.B. Bilker, S.J. **Siegel**, and R.C. Gur, *Levels-of-processing effect on word recognition in schizophrenia.* Biol Psychiatry, 2003. **54**(11): p. 1154-61.
14. **Siegel**, S.J., P. Connolly, Y. Liang, R.H. Lenox, R.E. Gur, W.B. Bilker, S.J. Kanes, and B.I. Turetsky, *Effects of strain, novelty, and NMDA blockade on auditory-evoked potentials in mice.* Neuropsychopharmacology, 2003. **28**(4): p. 675-82.
15. Connolly, P.M., C. Maxwell, Y. Liang, J.B. Kahn, S.J. Kanes, T. Abel, R.E. Gur, B.I. Turetsky, and S.J. **Siegel**, *The effects of ketamine vary among inbred mouse strains and mimic schizophrenia for the P80, but not P20 or N40 auditory ERP components.* Neurochem Res, 2004. **29**(6): p. 1179-88.
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17. Gould, T.J., S.P. Bizily, J. Tokarczyk, M.P. Kelly, S.J. **Siegel**, S.J. Kanes, and T. Abel, *Sensorimotor gating deficits in transgenic mice expressing a constitutively active form of Gs alpha.* Neuropsychopharmacology, 2004. **29**(3): p. 494-501.
18. Gur, R.E., C. Kohler, B.I. Turetsky, S.J. **Siegel**, S.J. Kanes, W.B. Bilker, A.R. Brennan, and R.C. Gur, *A sexually dimorphic ratio of orbitofrontal to amygdala volume is altered in schizophrenia.* Biol Psychiatry, 2004. **55**(5): p. 512-7.
19. Irani, F., M. Dankert, C. Brensinger, W.B. Bilker, S.R. Nair, C.G. Kohler, S.J. Kanes, B.I. Turetsky, P.J. Moberg, J.D. Ragland, R.C. Gur, R.E. Gur, and S.J. **Siegel**, *Patient attitudes towards surgically implantable, long-term delivery of psychiatric medicine.* Neuropsychopharmacology, 2004. **29**(5): p. 960-8.
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21. Maxwell, C.R., S.J. Kanes, T. Abel, and S.J. **Siegel**, *Phosphodiesterase inhibitors: a novel mechanism for receptor-independent antipsychotic medications.* Neuroscience, 2004. **129**(1): p. 101-7.
22. Ragland, J.D., R.C. Gur, J. Valdez, B.I. Turetsky, M. Elliott, C. Kohler, S. **Siegel**, S. Kanes, and R.E. Gur, *Event-related fMRI of frontotemporal activity during word encoding and recognition in schizophrenia.* Am J Psychiatry, 2004. **161**(6): p. 1004-15.
23. Talbot, K., W.L. Eidem, C.L. Tinsley, M.A. Benson, E.W. Thompson, R.J. Smith, C.G. Hahn, S.J. **Siegel**, J.Q. Trojanowski, R.E. Gur, D.J. Blake, and S.E. Arnold, *Dysbindin-1 is reduced in intrinsic, glutamatergic terminals of the hippocampal formation in schizophrenia.* J Clin Invest, 2004. **113**(9): p. 1353-63.
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27. Hans, M., K. Shimoni, D. Danino, S.J. **Siegel**, and A. Lowman, *Synthesis and characterization of mPEG-PLA prodrug micelles.* Biomacromolecules, 2005. **6**(5): p. 2708-17.
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29. Ragland, J.D., R.C. Gur, J.N. Valdez, J. Loughead, M. Elliott, C. Kohler, S. Kanes, S.J. **Siegel**, S.T. Moelter, and R.E. Gur, *Levels-of-processing effect on frontotemporal function in schizophrenia during word encoding and recognition.* Am J Psychiatry, 2005. **162**(10): p. 1840-8.
30. **Siegel**, S.J., C.R. Maxwell, S. Majumdar, D.F. Trief, C. Lerman, R.E. Gur, S.J. Kanes, and Y. Liang, *Monoamine reuptake inhibition and nicotine receptor antagonism reduce amplitude and gating of auditory evoked potentials.* Neuroscience, 2005. **133**(3): p. 729-38.
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33. **Siegel**, S.J., F. Irani, C.M. Brensinger, C.G. Kohler, W.B. Bilker, J.D. Ragland, S.J. Kanes, R.C. Gur, and R.E. Gur, *Prognostic variables at intake and long-term level of function in schizophrenia.* Am J Psychiatry, 2006. **163**(3): p. 433-41.
34. Roalf, D.R., B.I. Turetsky, K. Owzar, C.C. Balderston, C.M. Brensinger, R.E. Gur, S. **Siegel**, and P.J. Moberg, *Unirhinal Olfactory Deficits in Patients with Schizophrenia and First-Degree Relatives.* Journal of Neuropsychiatry and Clinical Neurosciences, 2006. **18**: p. 389-396.

35. Hahn, C.G., H.Y. Wang, D.S. Cho, K. Talbot, R.E. Gur, W.H. Berrettini, K. Bakshi, J. Kamins, K.E. Borgmann-Winter, S.J. **Siegel**, R.J. Gallop, and S.E. Arnold, *Altered neuregulin 1-erbB4 signaling contributes to NMDA> receptor hypofunction in schizophrenia.* Nat Med, 2006. **12**(7): p. 824-8.
36. Maxwell, C.R., Y. Liang, M.P. Kelly, S.J. Kanes, T. Abel, and S.J. **Siegel**, *Mice expressing constitutively active Gsalpha exhibit stimulus encoding deficits similar to those observed in schizophrenia patients.* Neuroscience, 2006. **141**(3): p. 1257-64.
37. Moberg, P.J., S.E. Arnold, R.L. Doty, R.E. Gur, C.C. Balderston, D.R. Roalf, R.C. Gur, C.G. Kohler, S.J. Kanes, S.J. **Siegel**, and B.I. Turetsky, *Olfactory functioning in schizophrenia: relationship to clinical, neuropsychological, and volumetric MRI measures.* J Clin Exp Neuropsychol, 2006. **28**(8): p. 1444-61.
38. **Siegel**, S.J., J.B. Kahn, K. Metzger, K.I. Winey, K. Werner, and N. Dan, *Effect of drug type on the degradation rate of PLGA matrices.* Eur J Pharm Biopharm, 2006. **64**(3): p. 287-93.
39. Irani, F., S.M. Platek, I.S. Panyavin, M.E. Calkins, C. Kohler, S.J. **Siegel**, M. Schachter, R.E. Gur, and R.C. Gur, *Self-face recognition and theory of mind in patients with schizophrenia and first-degree relatives.* Schizophr Res, 2006. **88**(1-3): p. 151-60.
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41. Phillips, J.M., R.S. Ehrlichman, and S.J. **Siegel**, *Mecamylamine blocks nicotine-induced enhancement of the P20 auditory event-related potential and evoked gamma.* Neuroscience, 2007. **144**(4): p. 1314-23.
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Abstracts: (Please list only those in the past 3 years.)

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Alternative Media: None

1: J Pharm Pharmacol. 1995 Feb;47(2):108-14.

Links

Preparation and characterization of 5-fluorouracil-loaded microparticles as biodegradable anticancer drug carriers.

Boisdron-Celle M, Menei P, Benoit JP.

Laboratoire de Pharmacie Galénique et Biophysique Pharmaceutique, Faculté de Pharmacie, Angers, France.

To provide a device releasing 5-fluorouracil in a controlled manner and injectable into the brain by stereotaxy, biodegradable poly ((+/-)-lactide-co-glycolide) (PLAGA) microparticles were prepared by an emulsion-extraction process. Although the solubility profile of the drug was not suitable for its encapsulation by the aforementioned method, careful choice of process variables allowed significant drug loading, reaching 30%. Thus, the size of the 5-fluorouracil crystals, the organic phase/aqueous phase ratio, the theoretical drug loading and the microparticle size played a predominant role. The microsphere size was adjusted to 20-40 microns by selecting the appropriate PLAGA and polyvinylalcohol concentrations, and the stirring rate of the initial emulsion. It was shown that the microparticle structure depended directly on the experimental conditions governing the precipitation rate of the coating material: two types of microparticles, I and II, were characterized. The morphology of the particles influenced the 5-fluorouracil-release patterns, as did other process parameters, such as the 5-fluorouracil crystal size and the PLAGA concentration. It was possible to sustain the 5-fluorouracil release over 18 days.

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